Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

For the reasons stated in this paragraph, it is applicants' understanding that the pending office action, mailed November 7, 2005, is a ***non-final*** office action. It is applicants' further understanding that the Office Action Summary accompanying the pending office action incorrectly indicated that the action was "final." Applicants' understanding of the status of the pending office action was confirmed during a telephone conversation between Examiner Goldberg and Andrew Gonsalves (applicants' legal representative) on December 5, 2005. In particular, Examiner Goldberg indicated that, since the office action contains new grounds of rejection, the office action is in fact a non-final action. On May 4, 2006, Examiner Goldberg again confirmed (by telephone message to Mr. Gonsalves) that the pending office action is a non-final action. Therefore, it is applicants' understanding that, by filing the present response/amendment with the U.S. Patent and Trademark Office ("USPTO") and by paying the necessary extension fees by the final deadline of May 8, 2006, applicants have satisfied their obligation for responding to the pending non-final office action, and no further action on the part of applicants at this time is required to keep the present application pending.

Claims 22 and 43-49 are hereby canceled without prejudice and claims 1 and 23 are hereby amended, so that claims 1-17, 21, 23, and 28-42 are now pending.

The rejection of claims 1-4, 9-17, 21, 28-30, 37, and 41 under 35 U.S.C. § 103(a) for obviousness over U.S. Patent No. 6,060,288 to Adams et al. ("Adams") in view of U.S. Patent No. 5,700,642 to Monforte et al. ("Monforte") is respectfully traversed in view of the above amendments and the following remarks.

Adams teaches a method of amplifying and detecting target nucleic acids using primers attached to a solid support. The USPTO has acknowledged that Adams fails to teach the 5'-Amino Modifier C6 spacer recited in independent claim 1 (Office Action, mailed November 7, 2005, at page 5). Monforte is cited as teaching the structure of the 5'-Amino Modifier C6 spacer and its use in making amino-modified oligonucleotides for attachment to a solid support. The USPTO has taken the position that it would have been obvious to combine the teachings of Adams and Monforte to practice the claimed method for detecting a

target nucleic acid molecule. For the reasons discussed below, applicants respectfully disagree.

Claim 1 has been amended to include the "hexaethylene glycol spacer" limitation contained in independent claim 22 (now canceled). This amendment finds descriptive support in original claim 22 and in the specification at page 11, lines 12-16, and page 18, line 30 to page 19, line 14. Because claim 22 is not covered by this rejection, applicants respectfully submit that this rejection is improper and should be withdrawn in view of the amendments to claim 1 (from which currently rejected claims 2-4, 9-17, 21, 28-30, 37, and 41 depend, either directly or indirectly). For this reason, applicants assert that no further argument is needed to overcome this rejection. However, even assuming *arguendo* that a *prima facie* case of obviousness could be made (which it cannot) for using the combination of the 5'-amino modifier coupled to the hexaethylene glycol spacer now recited in amended claim 1, applicants submit that such a *prima facie* case is clearly rebutted by the superior and unexpected results obtained from this combination.

Federal patent law recognizes that a *prima facie* case of obviousness can be overcome by showing evidence of superior or unexpected results. *See In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963); *In re Wiechert*, 370 F.2d 927, 152 USPQ 247 (CCPA 1967) (holding that a 7-fold improvement of activity of the claimed compound over the a prior art compound was sufficient to rebut a *prima facie* obviousness assertion based on close structural similarity of the compounds); MPEP § 2144.09, at 2100-165 (Rev. 3, Aug. 2005). Applicants respectfully submit that such superior and unexpected results are present in Examples 3-9 of the present application. As referred to in these examples, the combination of the 5'-amino modifier coupled to the hexaethylene glycol ("HEG") spacer is identified as either of the following: $F^{(HEG)}{}_n$ (where "n" is the number of units of HEG); aminoC6-(HEG); 5' HEG spacer; or 5'aminated $F^{(HEG)}$. In Example 1 (*see* Table 1, at page 26 of the specification), various primers and probes that were used to compare the effectiveness of the present invention are identified. In particular, the effectiveness of the combination of the 5'-amino modifier coupled with at least 10 thymidine molecules (referred to as "$F^{(dt)}{}_{10}$" and "5'$(dT)_{10}$") is directly compared to that of the aminoC6-(HEG) modifier of the present invention. Results of these comparisons are shown in Example 9, and provide evidence that

the aminoC6-(HEG) modifier of the present invention yields superior results over the 5'$(dt)_{10}$ spacer and 5'-linkers/spacers described in the prior art.

Specifically, Example 9 of the present application reports the solid phase-polymerase chain reaction ("SP-PCR") yield values from wells tethered with 5' HEG as compared to those from wells tethered with 5'$(dT)_{10}$. The HEG_5 spacer (of the present invention) was shown to have two-fold more fluorescence than the 5'$(dT)_{10}$ spacer (page 35, lines 16-20). Statistical analysis indicated that there were significant differences in the SP-PCR yields among the blank (control), 5'$(dT)_{10}$ spacer, and 5' HEG spacer (page 35, lines 16-20, 22-24, and page 36, lines 32-33). In particular, ANOVA results showed that the $(HEG)_5$ spacer resulted in a significantly greater yield than the $(dT)_{10}$ spacer ($p<0.0001$) and that the $(dT)_{10}$ spacer had significantly higher yield than the blank ($p<0.0001$) (page 35, lines 22-24; *see* Table 3, at page 36). Further, as described in the specification at page 36, line 33 to page 37, line 5, results showed that the protocol of the present invention resulted in a ***60-fold increase in extension*** of tethered oligonucleotides related to values reported in the prior art, particularly in Adessi et al., "Solid Phase DNA Amplification: Characterization of Primer Attachment and Amplification Mechanisms," *Nucleic Acids Research* 28:e87 (2000) (submitted herewith as **Exhibit 1**).

Applicants respectfully submit that the results reported in the specification (as summarized above) constitute superior and unexpected results over the cited art. Nowhere does Adams or Monforte, alone or in combination, report, teach, or suggest SP-PCR yields resulting from amplifying target nucleic acids using primers that are tethered to a solid surface using a 5'-amino modifier C6 spacer coupled to a hexaethylene glycol spacer. Thus, one of ordinary skill in the art would have no reasonable basis for combining the teachings of Adams and Monforte to achieve the superior and unexpected results reported in the present specification with respect to the SP-PCR yields achieved from the claimed invention of claim 1. Therefore, for the reasons described above, applicants respectfully submit that the rejection of claims 1-4, 9-17, 21, 28-30, 37, and 41 under 35 U.S.C. § 103(a) for obviousness over Adams in view of Monforte is improper and should be withdrawn.

The rejection of claim 5 under 35 U.S.C. § 103(a) for obviousness over Adams in view of Monforte and U.S. Patent No. 5,475,098 to Hall ("Hall") is respectfully traversed in view of the above amendments and the following remarks. The teachings and deficiencies

of Adams and Monforte are as described above. Further, the USPTO acknowledges that Adams and Monforte fail to teach detection of *Escherichia coli*. Thus, the USPTO cites Hall as teaching that *Escherichia coli* nucleic acids can be detected from biological samples using PCR and probes specific to the *Escherichia coli* nucleic acids. Claim 5 indirectly depends from amended claim 1. Nowhere does Hall teach or suggest the 5'-Amino Modifier C6 spacer coupled with the hexaethylene glycol spacer recited in amended claim 1. Because Adams and Monforte are deficient for the reasons noted above, and because Hall fails to overcome these deficiencies, the presently claimed invention would not have been obvious over Adams in view of Monforte and Hall. Therefore, the rejection of claim 5 should be withdrawn.

The rejection of claim 6 under 35 U.S.C. § 103(a) for obviousness over Adams in view of Monforte and U.S. Patent No. 5,489,513 to Springer ("Springer") is respectfully traversed in view of the above amendments and the following remarks. The teachings and deficiencies of Adams and Monforte are as described above. Further, the USPTO acknowledges that Adams and Monforte fail to teach detection of *Candida albicans*. Thus, the USPTO cites Springer as teaching that *Candida albicans* nucleic acids can be detected from biological samples using PCR and probes specific to the *Candida albicans* nucleic acids. Claim 6 indirectly depends from claim 1. Nowhere does Springer teach or suggest the 5'-Amino Modifier C6 spacer coupled with the hexaethylene glycol spacer recited in amended claim 1. Because Adams and Monforte are deficient for the reasons noted above, and because Springer fails to overcome these deficiencies, the presently claimed invention would not have been obvious over Adams in view of Monforte and Springer. Therefore, the rejection of claim 6 should be withdrawn.

The rejection of claim 7 under 35 U.S.C. § 103(a) for obviousness over Adams in view of Monforte and U.S. Patent No. 5,599,662 to Respess ("Respess") is respectfully traversed in view of the above amendments and the following remarks. The teachings and deficiencies of Adams and Monforte are as described above. Further, the USPTO acknowledges that Adams and Monforte fail to teach detecting human immunodeficiency virus (HIV). Thus, the USPTO cites Respess as teaching oligonucleotides useful for detecting HIV. Claim 7 indirectly depends from claim 1. Nowhere does Respess teach or suggest the 5'-Amino Modifier C6 spacer coupled with the hexaethylene glycol spacer

recited in amended claim 1. Because Adams and Monforte are deficient for the reasons noted above, and because Repess fails to overcome these deficiencies, the presently claimed invention would not have been obvious over Adams in view of Monforte and Respess. Therefore, the rejection of claim 7 should be withdrawn.

The rejection of claim 8 under 35 U.S.C. § 103(a) for obviousness over Adams in view of Monforte and U.S. Patent No. 5,792,609 to Wataya ("Wataya") is respectfully traversed in view of the above amendments and the following remarks. The teachings and deficiencies of Adams and Monforte are as described above. Further, the USPTO acknowledges that Adams and Monforte fail to teach detecting *Plasmodium ovale*. Thus, the USPTO cites Wataya as teaching oligonucleotides useful for detecting *Plasmodium ovale*. Claim 8 indirectly depends from claim 1. Nowhere does Wataya teach or suggest the 5'-Amino Modifier C6 spacer coupled with the hexaethylene glycol spacer recited in amended claim 1. Because Adams and Monforte are deficient for the reasons noted above, and because Wataya fails to overcome these deficiencies, the presently claimed invention would not have been obvious over Adams in view of Monforte and Wataya. Therefore, the rejection of claim 8 should be withdrawn.

The rejection of claims 31-36 under 35 U.S.C. § 103(a) for obviousness over Adams in view of Monforte and U.S. Patent No. 6,319,674 to Fulcrand et al. ("Fulcrand") is respectfully traversed in view of the above amendments and the following remarks. The teachings and deficiencies of Adams and Monforte are as described above. Further, the USPTO acknowledges that Adams and Monforte fail to teach using particular olefin monomers or particular substrates. Thus, the USPTO cites Fulcrand as teaching methods for covalently attaching ligands to a surface (e.g., glass, silica, magnesium sulfate, etc.), where the surface can be a solid substrate that has been functionalized with an amino group by reaction with an amine compound. Claims 31-36 indirectly depend from claim 1. Nowhere does Fulcrand teach or suggest the 5'-Amino Modifier C6 spacer coupled with the hexaethylene glycol spacer recited in amended claim 1. Because Adams and Monforte are deficient for the reasons noted above, and because Fulcrand fails to overcome these deficiencies, the presently claimed invention would not have been obvious over Adams in view of Monforte and Fulcrand. Therefore, the rejection of claims 31-36 should be withdrawn.

The rejection of claims 38-40 and 42 under 35 U.S.C. § 103(a) for obviousness over Adams in view of Monforte and U.S. Patent No. 5,728,526 to George ("George") is respectfully traversed in view of the above amendments and the following remarks. The teachings and deficiencies of Adams and Monforte are as described above. Further, the USPTO acknowledges that Adams and Monforte fail to teach using an extension reaction comprising dNTP, dITP, dUTP, or a particular polymerase. Thus, the USPTO cites George as teaching the use of an extension mixture containing dATP, dCTP, dTTP, dGTP, dITP, and dUTP for use in extending nucleic acid strands. Claims 38-40 and 42 directly or indirectly depend from claim 1. Nowhere does George teach or suggest the 5'-Amino Modifier C6 spacer coupled with the hexaethylene glycol spacer recited in amended claim 1. Because Adams and Monforte are deficient for the reasons noted above, and because George fails to overcome these deficiencies, the presently claimed invention would not have been obvious over Adams in view of George. Therefore, the rejection of claim 38-40 and 42 should be withdrawn.

The rejection of claims 22, 23, 43-47, and 49 under 35 U.S.C. § 103(a) for obviousness over Adams in view of U.S. Patent No. 6,255,050 to Nie ("Nie") is rendered moot with respect to canceled claims 22, 43-47, and 49, and respectfully traversed with respect to claim 23 in view of the above amendments and the following remarks. Claim 23 has been amended to now depend from independent claim 1. Thus, claim 23 (as amended) now requires that the primer be modified to include the 5'-Amino Modifier C6 spacer coupled with the hexaethylene glycol spacer recited in amended claim 1. The USPTO acknowledges that Adams does not teach the structure of the 5-Amino Modifier C6 spacer or the spacer phosphoramidite 18 recited in claim 22 (now canceled). To compensate for the deficiencies of Adams, the USPTO has cited Nie as teaching modifying two 18-mer oligonucleotides with 5'-amino group linkers. However, nowhere does Adams or Nie, alone or in combination, report, teach, or suggest SP-PCR yields resulting from amplifying target nucleic acids using primers that a tethered to a solid surface using a 5'-amino modifier C6 spacer coupled to a hexaethylene glycol spacer. Thus, one of ordinary skill in the art would have no reasonable basis for combining the teachings of Adams and Nie to achieve the superior and unexpected results reported in the present specification with respect to the SP-PCR yields achieved from the invention of claim 1 (from which rejected claim 23 now

depends). Therefore, for the reasons described above, applicants respectfully submit that the rejection of claims 22, 23, 43-47, and 49 under 35 U.S.C. § 103(a) for obviousness over Adams in view of Nie is improper and should be withdrawn.

The rejection of claim 48 under 35 U.S.C. § 103(a) for obviousness over Adams in view of Nie and George is rendered moot in view of the cancellation of claim 48.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

/Andrew K. Gonsalves, Reg. No. 48,145/

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Andrew K. Gonsalves
Registration No. 48,145

NIXON PEABODY LLP
Clinton Square, P.O. Box 31051
Rochester, New York 14603-1051
Telephone: (585) 263-1658
Facsimile: (585) 263-1600